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EXTENDED-SPECTRUM BETA-LACTAMASE AND CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE IN THE HEALTH CARE SETUP OF INDIA

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Abstract

The ever-evolving emergence of multidrug-resistant bacteria has brought mankind to the edge of a possible existential free fall. The designing of novel antibiotics to eradicate these deadly infections has been expertly countered by the remarkable adaptive capabilities of multidrug-resistant superbugs. The rapid horizontal dissemination of extended-spectrum β-lactamase (ESBL) and carbapenemase enzymes by nosocomial pathogens belonging to the gram-negative *Enterobacteriaceae* family is proving to be one of the biggest global public health threats, accompanied by grave clinical and economic impacts. The ability of these enzymes to hydrolyze the most advanced β-lactams imparts the carrier organisms resistance towards the newest of the cephalosporins, as well as the last resort carbapenems. Their frequent aminoglycoside and fluoroquinolone co-resistance has left us with a handful of treatment options, including the old antibiotics like colistin and fosfomycin. In India, most of the data related to the above-mentioned organisms are largely disorganized and, understandably, unclear. This review attempts to briefly discuss the ESBL and carbapenemases along with the summing up of the information regarding the emergence and transmission of ESBL and carbapenemase genes via the *Enterobacteriaceae* group in the Indian health setup, during the last decade, in a zone-wise manner. The incidences of infection by these enterobacteria, along with their ESBL and carbapenemase profiles, are discussed in detail based on the reports published by various national and global research teams from all corners of the country. The paper also highlights the need to report these organisms immediately after they are encountered in the clinics, for the prevention of their dissemination, as large information gaps seem to exist in specific regions of India.

Keywords: Nosocomial Infections; Superbugs; AMR; ESBLs

1. Introduction

A global pandemic caused by the SARS-CoV-2 virus has brought the medical fraternity to its knees. At this critical juncture, all the countries on this planet are overwhelmed with large numbers of active infections. Unfortunately, most of the attention, money, as well as research is now being diverted towards the containment of the Coronavirus. Although this scenario is completely justified, we must not forget the threat of antimicrobial resistance (AMR), which is also moving on an upward trajectory. The overuse, misuse, and severe misconceptions about antibiotic usage have created a global public health problem that has been further accentuated in a developing country like India. The construction of multi-drug resistant (MDR) bacteria, either by the acquisition of multiple antibiotic resistance genes in mobile genetic elements (MGE) or the vertical chromosomal inheritance of resistance mutations, has created a huge hurdle in the management of severe drug-resistant gram-negative bacteria (GNB) infections worldwide [1, 2]. Of all the antibiotics that have been explored for their antimicrobial efficiency, the β-lactams are perhaps the most researched and exploited. The first β-lactams were the penicillins, which were sulfur-containing penams, closely followed by the discovery of the cephalosporins or the sulfur-containing cephems. What transpired next was a revolution in medical science with the extensive manipulation of the natural β-lactams to obtain a plethora of semi-synthetic and synthetic preparations like the monobactams, carbapenems, oxapenams, oxacephems, and carbacephems. GNB belonging to the *Enterobacteriaceae* family capable of synthesizing Extended-Spectrum Beta-Lactamases

(ESBL) and carbapenemases are on the rise, resulting in the destruction of these β-lactam antimicrobials, eventually resulting in prolonged hospital stays and a significantly high case-fatality rate [3]. These enzymes can hydrolyze the β-lactam ring of first, second, and third-generation cephalosporins, oxyimino-monobactams such as aztreonam, and last resort carbapenems like meropenem and imipenem [4-6]. The rapid appearance of ESBLs like TEM, SHV, CTX-M, PER, VEB, etc., among several GNB species in a short time is due to the phenomenon of natural selection, plasmid-mediated horizontal gene transfer (HGT), and vertically inherited chromosomally encoded characteristics [7]. All β-lactamases, including the ESBLs, share sequence resemblance with penicillin-binding proteins (PBPs), which hints towards their origin from such PBPs [8] in staging this biological mimicry. Due to the rapid plasmid and transposon-mediated transmissibility of these genes, they disseminate within phylogenetically diverse GNB genera, including the ones classified as *Enterobacteriaceae*, the *Pseudomonads*, *Haemophilus*, and *Neisseria*, to name a few [4, 5, 8] and are often found to promote co-resistance against other classes of antibiotics [9]. Along with the notoriety of the ESBLs, the advent of carbapenemase genes capable of hydrolyzing newer-generation carbapenems has rattled the medical fraternity [10-12]. Carbapenem-resistant enterobacteria (CRE), promoting co-resistance [13, 14], have taken the hospitals by storm and are disseminating rapidly, causing widespread treatment failure, both in the case of community-acquired as well as nosocomial infections [15]. India has been held responsible by various studies to be the source of ESBL dissemination. The odds ratio (OR), which signifies the risk of the onset of a specific drug-resistant infection, has been decisively shown to be very high for India by two independent studies for ESBL-positive*Escherichia coli* infections [16, 17]. One of the most infamous cases of carbapenemase-producing *Klebsiella pneumoniae* was observed in India in 2008 when a Swedish patient of Indian descent was infected with a superbug [14]. The organism was found to produce a novel metallo-β-lactamase, NDM-1, and was resistant to all known antibiotic classes except fluoroquinolones and colistin. NDM-1 was perhaps the perfect β-lactamase, as it was cogent in destroying all known β-lactams except aztreonam. The medical infrastructure of the hospitals and handling of these cases by the concerned medical personnel faced criticism as it was clear that NDM-1 did spread via patients who had received treatment in the Indian subcontinent [18, 19]. This incident made the Indian government take certain constructive actions related to AMR. Following Kingdon's three-stream policy window model [20], the Indian government took a series of steps to curb AMR, beginning with the formation of the national task force on AMR containment in 2010 and the adoption of the national policy for containment of AMR in the same year [21]. In the following year, AMR was included in the Jaipur declaration, and antimicrobial containment was included in the 12th 5-year plan. Unfortunately, despite having positive intentions, the implementation was poor, and little progress was made. The wheels started rolling again when the "Indian Council of Medical Research" or ICMR decided to get involved in 2012. They prompted the adoption of the Chennai declaration at the second annual conference of the Clinical Infectious Disease Society, the first-ever meeting of the medical societies of India on AMR [22]. The importance of this declaration lay in the fact that it adopted a more practical or "Indian" approach in AMR management, and resultantly, the initiative was lauded by national and international experts alike [22, 23]. The current Indian government has also made it clear that it will tackle AMR with an iron fist, leading to the adoption of a national action plan on AMR in 2017 (2017-2021) based on the AMR global action plan. The six strategic priorities devised under the plan are; 1) improving awareness and understanding of AMR through effective communication, education, and training; 2) strengthening knowledge and evidence through surveillance; 3) reducing the incidence of infection through effective infection prevention and control; 4) optimizing the use of antimicrobial agents in health, animals, and food; 5) promoting investments for AMR activities, research, and innovations; and 6) strengthening India's leadership on AMR [21, 24].

Post Independence, India has had high caseloads of infectious diseases like Malaria, Tuberculosis, Cholera, Typhoid, and AIDS. Along with it, the rapidly growing population has put a lot of pressure on the medical, agricultural, and food-producing sectors of the country [21]. The public health infrastructure is poor, with a high burden of various kinds of microbial infections, hugely exacerbated by poor sanitation conditions and malnutrition [25]. These factors have influenced people to ignore treatment altogether or self-medicate. Low cost, incorrect prescribing, and easy availability of high-end antibiotics have eventually led to the rise in resistance against cephalosporins, fluoroquinolones, and carbapenems, resulting in a significant negative socio-economic and financial impact on the low and middle-class population of India. This review

focuses on the incidences of ESBL and carbapenemase infections by *Enterobacteriaceae* in Indian rural and urban hospitals, which should give us an idea of the upcoming challenges that we must tackle to save India from an impending catastrophe. It is incorrectly anticipated that in a populous country like ours, there will be a large volume of relevant literature. During our research and drafting of this manuscript, we found it to be quite the opposite. This review is the first of its kind to sum up the incidences of ESBL and carbapenemase-producing nosocomial *Enterobacteriaceae* infections in India and attempts to fill the gaps in the

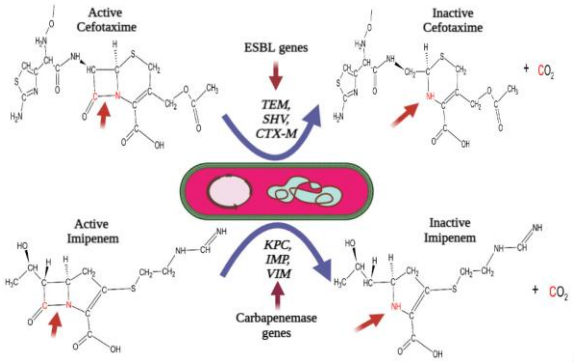

Figure 1: Mechanism of action of ESBLs and carbapenemases involving the opening of the β-lactam rings of the β-lactam antibiotics; the arrows indicate the precise location of bond hydrolysis to eventually release one molecule of CO_2, inactivatingthe antibiotic in the process.

2. ESBLs: in brief

Before learning about ESBLs in detail, the reaction they catalyze must be clear to the readers. The transpeptidase enzymes (adenyl-alanine endopeptidases) responsible for the peptidoglycan cross-linking of the bacterial cell wall act by the acylation of susceptible nucleophilic motifs like the peptidoglycan D-Ala-D-Ala-D-Ala tripeptide. Upon performing the serine acylation half-reaction, one terminal D-Ala is released, followed by the attachment of the residual D-Ala-D-Ala dipeptide to an amine substituent of the neighboring peptidoglycan strand via the deacylation half-reaction. β-lactams employ deceptive molecular mimetics whereby they allow the transpeptidase to perform the primary acylation reaction but disallow the deacylation, forming a dead-end complex [26, 27]. This severely disrupts the cellular homeostasis of the bacteria, resulting in the activation of cell wall-destroying proteins known as autolysins, ultimately causing the loss of cell wall integrity. Once the cell wall is impaired in such a manner, the bacteria perish as they fail to reproduce and contain the internal osmotic pressure of the cell [28, 29]. From the bacterium's point of view, it can save itself by employing one of two possible ways. It can either prevent the mimetic acylation half-reaction of the β-lactam by mutational alteration of the transpeptidase or it can produce drug-scavenging enzymes that employ their own mimicry to disguise themselves as transpeptidases, followed by binding to β-lactams by acylationand destroying them by deacylation of the ring structure, thereby opening it (Figure 1). The ESBLs do exactly that (Figure 2).

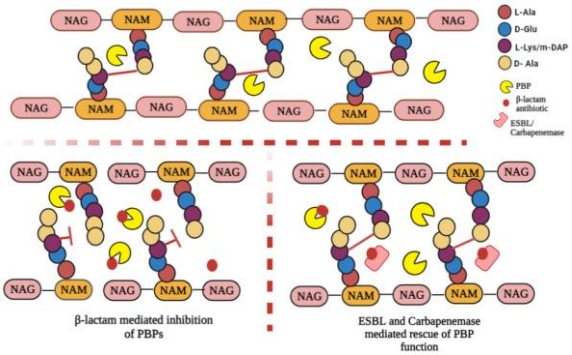

Figure 2: Counterclockwise from top: Peptidoglycan cross-linking catalyzed by the transpeptidases (PBPs), between adjacent layers of peptidoglycan under normal circumstances (top); Inhibition of PBP action by the β-lactam antibiotics employing molecular mimetics leading to a β-lactam-PBP deadlock (bottom-left); Rescue of PBP activity by the ESBLs/carbapenemases by counter-mimicry, leading to the opening of the β-lactam rings of the antibiotics, causing inactivation (bottom-right).

As mentioned earlier, the ESBLs are a class of β-lactamases belonging to Class A according to the Ambler classification scheme. The Ambler classification scheme divides β-lactamases into four distinct groups, i.e., A to D. Protein homology is the main parameter of classification according to this scheme, where the A, C, and D groups are serine β-lactamases, whereas group B harbors the metallo β-lactamases. A more practical and medically relevant classification scheme was devised by the trio Bush-Jacoby-Medeiros [30]. They classified all β-lactamases into four major groups and multiple subgroups according to their substrate preferences or inhibitor profiles. According to their grouping, the ESBLs fall under group 2be. Group 2b houses the entire set of progenitor β-lactamases like TEM-1, TEM-2, and SHV-1. The 'e' in the 2be represents the derivative β-lactamases from the progenitors, differing minutely from them (up to one amino acid) but with an extended spectrum of activity. These little alterations in the protein homology cause a massive change in the hydrolyzing capabilities of these enzymes, making them capable of destroying potent targets like the third-generation cephalosporins or aztreonam. The only sets of

ESBLs belonging to a different group are the OXA enzymes, placed in 2d.

2.1 TEM β-lactamases:

The TEM β-lactamases were first encountered in Athens, Greece, where an *E.coli* isolate was found to harbor the gene. The bacterium was isolated from a patient named Temoniera, making way for the designation of the enzyme as TEM-1 [31]. This enzyme wreaked havoc in the clinical setting by spreading to a wide range of gram-negative pathogens, including enterobacteria. TEM-1 could hydrolyze most of the natural penicillins, semi-synthetic penicillins like ampicillin, as well as the early generation cephalosporins. This widespread presence of TEM-1 and its close derivatives TEM-2 and TEM-13 [32]was the primary reason that prompted the pharmaceutical fraternity to release the oxyimino or 3rd generation cephalosporins to the market [33]. The bulky oxyimino side chain at the C7 position of the drugs made it difficult for the enzymes to accommodate them in their active site [34]. In 1987, France, the bacterial reply to the 3rd generation cephalosporins was first encountered, where *K. pneumoniae* isolates harboring a plasmid encoded β-lactamase were detected, which had enhanced cefotaxime hydrolysis capability [35, 36]. Preliminarily named CTX-1, this enzyme was found to differ from the TEM-2 enzyme by just two amino acid substitutions and thus was renamed TEM-3 [37], which is considered the first true ESBL. More than 100 TEM enzymes have since been reported worldwide, of which most are ESBLs [38]. Going against the definition of ESBLs, some clavulanic acid-resistant TEM enzymes are being unearthed and are being called the complex mutants of TEM [36, 39-41], which may represent the next step in the evolution of β-lactamases.

2.2 SHV β-lactamases:

In the 1970s, another formidable threat to the 3rd generation cephalosporins surfaced in *E. coli*, known as SHV-1 β-lactamase [42]. The SHV enzymes are the most frequently encountered clinical ESBLs [43], where the name SHV denotes the 'sulfhydryl variable'. This SHV-1 enzyme possessed promising activity against the penicillins and the first-generation cephalosporins [44] and had probably originated from a primordial chromosomal gene of *K. pneumoniae* [45], although its mode of mobilization into plasmids and MGEs (like the conjugative plasmid p453) is not clear [46, 47]. Like TEM-1, SHV-1 was not a true ESBL due to its inability to hydrolyze the 3rd generation cephalosporins. In 1983, Germany, a *Klebsiella ozaenae* isolate was obtained which could tolerate cefotaxime efficiently, and to a lesser extent ceftazidime due to its possession of a β-lactamase

which had a single amino acid substitution compared to SHV-1 (the glycine at position 238 was substituted with a serine) [48]. This enzyme, named SHV-2, was a potent ESBL and is disseminated to every inhabitable continent on this planet in the next 15 years [49]. One of the most extensive reviews on SHV β-lactamases by Liakopoulos *et al*. has claimed that till 2016, 189 allelic variants of the SHV enzymes have been documented, which have been shown to resist 3rd generation cephalosporins, monobactams, and carbapenems [42, 50]. They are predominantly present in *Salmonella enterica*, *E. coli*, and other bacterial strains under the *Enterobacteriaceae* family [8]. The appearance of SHV member genes among hospital-borne pathogens like *K. pneumoniae*, able to withstand penicillin, cephalosporins, and monobactams [12], is becoming a serious threat to public health, especially in an LMIC country like India.

2.3 CTX-M β-lactamases:

In 1989, a cefotaxime-resistant *E.coli* strain was isolated in Germany that produced some form of ESBL distinct from TEM and SHV and was named CTX-M-1due to its cefotaxime hydrolysis capability [51]. A similar non-TEM and non-SHV enzyme was encountered three years previously in Japan [52], but was named FEC-1 as it was isolated from the fecal flora of a laboratory dog. By the end of the 1980s and the beginning of the 1990s, other similar enzymes began to surface in GNB [53, 54]. These efficient cefotaxime hydrolyzing enzymes had alkaline pI values, were less efficient against ceftazidime, and were susceptible to β-lactamase inhibitors like clavulanic acid and tazobactam. In 1989, an *E.coli* isolate harboring the same enzyme type was clinically encountered in France and was named MEN-1[55]. Barthélémy *et al.* sequenced the enzyme in the same year to find out that it had very little identity (39%) with the TEM and SHV enzymes, making it the first member of the non-TEM, non-SHV class of plasmid encoded ESBLs [56]. In 1996, it was finally resolved that MEN-1 and CTX-M-1 were the same enzymes and a variant of Toho-1 or CTX-M-2 [57]. Since then, the CTX-M family of enzymes has become the most widely spread ESBLs in the gram-negative realm [58]. Believed to have originated from the chromosome of the intrinsically resistant *Kluyvera* sp. [59, 60], there are currently more than 40 CTX-M enzymes known, subdivided into 5 clusters [61], and the numbers are going up every day.

2.4 OXA, PER, and other ESBLs:

Other ESBLs detected in various nosocomial bacterial species are mentioned in Table 1.

Table 1: ESBLs other than TEM, SHV, CTX-M, and OXA detected in various nosocomial bacteria worldwide

Bacterial species	Detected ESBL	Closest relative	Country of origin	Reference
P. aeruginosa	OXA-10	-	-	[62]
P. aeruginosa	OXA-11, OXA-14, OXA-16, OXA-17	OXA-10	Turkey	[8]
P. aeruginosa	OXA-13 OXA-19, OXA-28	OXA-10	France	[63, 64]
P. aeruginosa	OXA-15	OXA-2	Turkey	[65]
P. aeruginosa	OXA-18	OXA-9, OXA-12	France	[66]
Salmonella enterica serovar Typhimurium	PER-1	-	Argentina	[67]
E. coli	VEB-1	chromosomal cephalosporinases in *Bacteroides* spp., PER-1, PER-2	Vietnam	[68]
E. coli	TLA-1	CME-1	Mexico	[69]
Enterobacter cloacae	SFO-1	AmpA of *Serratia fanticola*	Japan	[70]

3. Carbapenemases: an overview

The application of carbapenems is the last expedient for the management of AMR throughout the world. However, the rapid dissemination of carbapenem resistance genes is becoming a serious concern. As discussed previously, the mechanism of action of the carbapenemases is like other β-lactamases and will not be discussed in this section. Bacteria surviving in the presence of the carbapenem class of antibiotics give rise to the term carbapenem resistance (CR). According to the US Centers for Disease Control and Prevention (CDC) report, the minimum inhibitory concentration (MIC) of≥ 4 µg/ml against doripenem, meropenem, or imipenem and ≥ 2 µg/ml against ertapenem defines the CRE, perhaps the most resilient group of nosocomial pathogens known to humankind [71, 72]. The frequently employed method by CRE for gaining CR is the synthesis of carbapenemase enzymes, the hydrolyzing enzymes that efficiently break down the β-lactam ring of carbapenems [73]. According to the Ambler classification, carbapenems belong to the class A and D serine β-lactamases and class B metallo-β-lactamases (MBLs). When classified using the Bush-Jacoby-Medeiros scheme, they fall under classes 2f, 2df, and 3, respectively [74].

3.1 Class A/2f carbapenemases:

Among the class A type, *Klebsiella pneumoniae* carbapenemase (KPC), first reported in *Klebsiella pneumoniae* in 2001 [75], is predominantly been detected in America, southern Europe, Israel, and China and has rapidly disseminated via a plasmid [76] to other GNB including *Enterobacter* sp., *E. coli*, *Salmonella* sp., *Serratia* sp., *Pseudomonas aeruginosa*, and *Pseudomonas putida*[6, 77]. Other prominent members of the class include imipenemase/non-metallocarbapenemase-A (IMI/NMC-A), Guiana extended-spectrum (GES) β-lactamase, *Serratia marcescens* enzyme (SME), and *Serratia fanticola* (SFC) carbapenemase [75, 78-81]. All these enzymes mentioned above are characteristically susceptible to β-lactamases inhibitors like clavulanic acid and tazobactam, which is the precise reason for their placement in the 2f group according to Bush-Jacoby-Medeiros [74]. As far as homology and occurrence are concerned, SFC-1 and SME are closely related to the KPC enzymes. SME and IMI/NMC-A are chromosomally encoded, whereas GES is produced via an integron housed by *P. aeruginosa* [82].

3.2 Class D/2df carbapenemases:

OXA enzymes or oxacillinases capable of hydrolyzing β-lactams are described in Ambler Class D. Like Ambler Class A and C β-lactamases, they have a serine at their active site for catalysis. Just like the Class A enzymes, they have retained the motif S-X-X-K, where S is the active site serine. The other two common motifs between the Class A and Class D enzymes are the Y-G-N/S triad and K-T-G triad [83]. A subset of that group is capable of

opening up carbapenems and is suitably placed under group 2df by Bush-Jacoby-Medeiros [74]. These OXA enzymes have mainly been detected in the chromosomes of certain *Acinetobacter baumannii* strains [84] but invasive variants like OXA-48 are plasmid-borne and can be found in *K. pneumoniae*, *E. coli*, *Citrobacter freundii*, and *Enterobacter cloacae*[85]**.** The appearance of an enzyme-like OXA-48 is of great concern as they are resistant to almost all β-lactam inhibitors available in nature [86] and can wreak havoc in combination with ESBLs. Additionally, it has the exceptional ability to mutate rapidly and enlarge its resistance spectrum. OXA-48 can completely resist the function of penicillins and shows medium and intermediate activity against carbapenems and cephalosporins, respectively[73]. Apart from OXA-48, other variants like OXA-162, OXA-163, OXA-181, OXA-204, and OXA-232 are widespread in genera like *Pseudomonas*, *Shewanella*, *Burkholderia*, and *Acinetobacter*[85, 87].

3.3 Class B /3 MBLs as carbapenemases:

Both the two previously described classes of carbapenemases i.e., Class A and D, were serine enzymes. What sets this specific class apart from the other two is the presence of one or two Zn^{2+} ions at the active center [88]. On being MBLs, these carbapenemases were given their own class by Bush-Jacoby-Medeiros, Class 3. As far as genetic transmissibility is concerned, the genes encoding these enzymes were found to be extremely versatile as they were found to be residents of integrons, plasmids, chromosomes, and transposons [74]. Despite being powerful β-lactam hydrolyzers, these enzymes have an obvious weakness. Their dependence on the active site divalent metal ion for catalysis often spells doomsday as they are inactivated by simple metal chelators like ethylenediaminetetraacetic acid or EDTA. These genes, often found in bacterial integrons, integrate into the host genome via typical *attI* and *attC* mediated site-specific recombination, followed by transcription from an MGE contained promoter inserted in the integrase gene [89-91].

A variety of MBL carbapenemases have been described in the literature to date. The most prominent ones are Florence Imipenemases (FIM), Germany imipenemases (GIM), Sao Paolo metallo-β-lactamases (SPM), New Delhi metallo-β-lactamases (NDM), Verona integrated-encoded metallo-β-lactamases (VIM), and Imipenemases (IMP) [14, 92-96]. Unearthed in the 1990s, IMP and VIM are considered true MBLs and have given rise to a multitude of transmissible variants via mutations [95, 97]. These variants, like IMP-6 and IMP-1, have varying activity towards doripenem, meropenem, and imipenem due to the nature of the mutations present [98]. For instance, the *P. aeruginosa* VIM-4 with an inserted arginine at position 44 and a serine to arginine substitution at position 265, has substantially greater carbapenem hydrolysis ability compared with VIM-1 [99]. A similar story has been observed in IMP-6, which differs from IMP-1 by a single amino acid substitution i.e., serine to glycine at position 214, but has significantly higher activity against meropenem. This had made IMP-6 an essential asset in the drug resistance arsenal of CRE and *P. aeruginosa* [100, 101]. From the Indian perspective, however, the most infamous MBL/carbapenemase has been NDM-1. NDM-1, the first of the NDM enzymes, was first isolated from New Delhi, India, and has been held responsible for the generation of NDM-producing bacteria[102]. Since then, these enzymes have disseminated to other parts of the world, including the United States and Europe, via travelers. NDM is mainly produced by CRE, like *K. pneumoniae* and *E. coli*[103]. Elegant studies have identified that the plasmid encoding NDM-1 also confers co-resistance against quinolones and aminoglycosides [103]. Unlike most other MBL carbapenemases, NDM-1 is largely plasmid-borne and does not disseminate via integrons [74].

4. The Indian Scenario:

According to the World Health Organization or WHO, Nosocomial infections can be defined as “An infection acquired in a hospital by a patient who was admitted for a reason other than that infection. An infection occurring in a patient in a hospital or other health care facility in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and occupational infections among staff of the facility” (Figure 3) [104]. Startlingly, Dr. Soumya Swaminathan, who served as the ICMR chief and is currently the chief scientist at the WHO, admitted in an article published in the British Medical Journal that India does not have accurate estimates of its nosocomial burden [105]. This confession added credibility to another publication of 2015 that claimed that the rate of contracting nosocomial infections, as well as the prevalence of AMR in India, is significantly higher than that reported by the Centers for Disease Control and Prevention (CDC) [106]. Remedial action was then initiated by the ICMR with the release of the hospital infection control guidelines in 2019 [107]. Focusing mainly on organisms like *P.aeruginosa*, *Clostridium difficile*, MRSA, and *A. baumannii*, not a single line was spent on ESBL-producing*Enterobacteriaceae* and CRE,despite multiple reports of emerging ESBL-producing*Enterobacteriaceae* and Carbapenem-

resistant *Enterobacteriaceae* from India, published in reputed international journals [108-112].Let us explore how these organisms have created a magnanimous crisis in Indian hospitals in the last decade and deserve more attention from the public health administration in India. With a rapidly growing volume of literature, only the papers we assessed to be significant were reviewed.

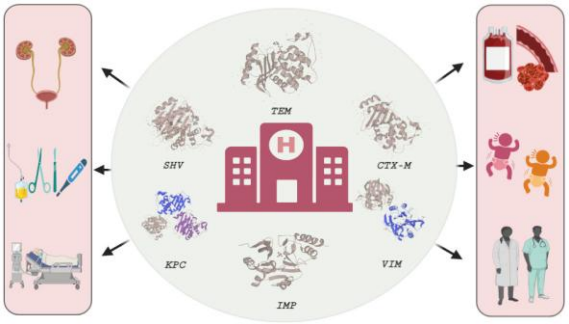

Figure 3: Possible routes of dissemination of ESBL-producing *Enterobacteriaceae* and Carbapenem-resistant *Enterobacteriaceae* in the hospital/health-care setting.

5. ESBL-producing *Enterobacteriaceae* (EPE) and Carbapenem-resistant *Enterobacteriaceae* (CRE) mediated nosocomial infections in India:

5.1 Neonatal Sepsis:

In 2015, Molyneux and Gest suggested in a paper that of all the 2.6 million neonates that don't survive their first month of life globally, 670,000 of them die due to sepsis [113]. The number is 30 deaths per 1000 live births in India, which is frightening [114]. The newborn children have decreased immune cell activity at birth with underdeveloped complement systems [115]. They do not possess preferential anti-inflammatory responses with poor immunologic memory. This makes them extremely vulnerable to a plethora of hospital-borne superbugs, resulting in early (< 72 hrs) or late (>72 hrs) sepsis.

In Aligarh, North India, Shakil and team reported 16 infections and 139 colonizations out of 238 neonates studied in 2010 by ESBL-producing*K. pneumoniae* and *E. coli*. 3 of the *E. coli-infected* neonates succumbed to their infection [116]. High CTX-M-15 carriage in neonates was reported in diverse clones of *K. pneumoniae* and *E. coli* by Roy *et al.* (2013), indicating rapid dissemination via HGT [117]. The Delhi Neonatal Infection Society (DeNIS) presented a more rigorous dataset from New Delhi in 2016 from three tertiary care neonatal units [118]. Out of the 13530 neonates who participated in the study, 1934 of them were given a final diagnosis of sepsis. MDR *K. pneumoniae* and *E. coli* resistance towards extended-spectrum cephalosporins and carbapenems made their presence felt among all the isolated pathogens. A similar outborn cohort study by Jajoo *et al.* (2018) was published from New Delhi, where the data of one of the DeNIS hospitals, Chacha Nehru Bal Chikitasalaya, was reported (was excluded in the previous DeNIS study) [119]. Out of the 1416 sepsis diagnosed episodes, 72.1%, 30%, and 58.3% resistance towards carbapenems was obtained for *K. pneumoniae*, *E. coli*, and *E. cloacae*, respectively. The dominance of CRE enterobacteria in North Indian neonatal ICUs was perhaps best understood from the results obtained by Ahmad *et al.* (2018), where they reported a staggering 41.06 % resistance to carbapenems. *E. coli* (45.5%), *K. pneumoniae* (40.9%), *C. freundii* (4.5%), *Citrobacter braakii* (2.3%), *Klebsiella oxytoca* (2.3%), *E. cloacae* (2.3%), and *Enterobacter aerogenes* (2.2%) were the major CRE identified and found to possess different variants of the NDM, OXA, SHV, and CMY genes [120].

Going south, the threats posed by ESBL-producing*K. pneumoniae* as well as CRE on neonatal health have been documented [121-124]. In 2010, Zakariya *et al.* published a 2-year study from JIPMER, Pondicherry, where they found that *K. pneumoniae* was the most predominant organism causing early as well as late-onset sepsis [125]. Out of all the *K. pneumoniae* isolates, 32 % were ESBL producers. The fact that most of the neonates suffering from sepsis were inborn suggested that ESBL non-producing, as well as producing *K. pneumoniae*,were common pathogens found in the neonatal ICUs and nurseries [126]. The standard treatment regimen followed for these cases was imipenem/meropenem in combination with an aminoglycoside. This was because another study from Chennai reported very high sensitivities of amikacin, gentamicin, and imipenem against ESBL-negative as well as positive *K. pneumoniae* in treating neonatal septicemia [127]. The rise in carbapenem resistance was reported in 2014 from Chennai itself,whereof all the neonatal sepsis isolates, 14.4 % were found to be carbapenem-resistant, with significant representation of *K. pneumoniae* and *E. coli*. The ability to hydrolyze carbapenems was correlated with increased neonatal mortality, which was alarming [122]. Even then, articles from Pondicherry, Mangalore, and Mysore suggest that CRE causing neonatal sepsis is contained to a certain extent in this part of the country. Both teams suggested that the main emphasis must be given to control and minimize ESBL-producing*Enterobacteriaceae* (EPE) infections in neonatal wards, as 66.7 % and 39 % of all tested isolates produced ESBL [128, 129].

Moving eastwards, prominent research data reporting neonatal sepsis has been scarce. Nevertheless, a few papers published from this region deserve mention. In 2014, a team from

Kolkata reported the first study on emerging CRE in a neonatal ICU for an extended period of time[130]. 14 % of all the sepsis-causing enterobacteria were found to possess the NDM-1 MBL. This team had previously reported two of the very early cases of neonatal NDM-1 in this country [131]. ESBL variants, namely, CTX-M (gr-1), TEM, and SHV were found in 82 %, 70 %, and 45 % of all the isolates, respectively. The most worrisome observation was the co-resistance facilitated by the NDM-1 gene against aminoglycosides and quinolones via the *armA*/*rmtB* and *aac(6')-Ib-cr* genes residing in highly mobile genetic elements like Class I integrons. This study preceded similar studies reported from Assam and Tripura. The first study by Devi *et al.* (2018) reported the presence of ESBL and carbapenemase-producing *Klebsiella* (OXA, SHV, TEM, and NDM-1) and *E. coli* (SHV and NDM-1) from suspected neonatal meningitis patients [132]. The second one reported the carriage of the NDM-1 gene in 4 different clones or sequence types of virulent *K. pneumoniae*[133]. The result that stood out from this paper was the carriage of the NDM-1 gene in association with IS*Aba125* or IS*Ec33* elements housed in large conjugative plasmids of IncF type, which was in accordance with one of their previous publications [134]. The latest reports of hypervirulent *K. pneumoniae* harboring carbapenemase genes like NDM-1 and OXA-48 in IncFI plasmids [135] or the presence of NDM-1, NDM-5, and VIM-6 genes in BERNARDS *K. pneumoniae* from the region are worrisome [136], as in cases like these, the mortality is generally high.

The western part of India has a comparatively smaller number of publications reporting EPE and CRE in neonatal sepsis. Ironically, in a multicentric study investigating the role of ESBL-producing bacteria in neonatal sepsis, Chandel *et al.* (2011) reported the highest percentage of ESBL harborers from Mumbai, the busiest city in western India [137]. *K. pneumoniae* (30.97 %) and *E. coli* (33.34 %) were the predominant ESBL-producing organisms from all sites taken together, and the highest percentage of ESBL producers among individual sampling locations was found to be Mumbai with 33 %. In Pune, Muley *et al.* (2015) reported slightly lower loads of ESBL-producing*K. pneumoniae* and *E. coli* at 29.4 % and 25 % respectively, with 100 % sensitivity towards imipenem [138]. They showed concern that due to high ESBL incidences, medical personnel have been forced to use old antibiotics like colistin, which may result in the rise in carbapenem-colistin co-resistance [139]. Umate *et al.* practically accepted that there is a paucity of data related to neonatal sepsis from Western India [140]. Published in 2019, the study did not report the presence of EPE or CRE in the infected neonates but showed that *Klebsiella* was the second most common organism causing neonatal meningitis. We sincerely hope that quality publications will come out from the western states of the country related to the incidences of EPE and CRE in neonatal sepsis soon. In all certainty, it will help shape the treatment strategies against the superbugs, which in turn, will give those ill-fated children a chance to survive.

5.2 Urinary Tract Infections (UTIs):

Urinary tract infection or UTI is a collective term for all infections of the urinary tract, starting from the kidneys to the urethra. They may manifest as simple urethral cystitis to a life-threatening condition, pyelonephritis. UTIs are the most frequently encountered clinical infections in the world, accounting for 30 % of all nosocomial infections [141]. It has been estimated that approximately 150 million people, or more precisely, 17.5 per 1000 people, suffer from UTIs per year worldwide, where adult females have been found more than 30 times more susceptible than adult males (below the age of 50) [142-144]. In UTI-induced bacteraemic episodes, the mortality may range from 4 % - 30% and greatly depends on the age, treatment urgency, or associated co-morbidities of the patient [145]. Without going into details about the different kinds and types of UTIs, let us discuss the current literature available about EPE and CRE-induced UTIs in Indian hospitals.

It must be understood that there is a very delicate interplay between environmental and nosocomial organisms. As a matter of fact, most nosocomial superbugs make their way into the hospital via community-acquired infections. Akram *et al.* (2011) reported the very first case of community-acquired genomic CTX-M in *E. coli* in Aligarh, showing how MGEs like class I integrons are crucial in the dissemination of MDR among closely or distantly related GNB in the environment [146]. In the hospital setting, there is always the possibility of further selection of these organisms, creating treatment hurdles. The positive correlation of high % ESBL production by organisms like *E. coli*, *K. pneumoniae*, and *Enterococcus* sp. with MDR has been reported in two studies (36.8 % and 45.1 % respectively) from this region [147, 148]. There is a high probability that, on making further molecular inquest, these investigators could have unearthed more such integrons or MGEs associated with the MDR phenotype. In a vast country like India, due to the unavailability of resources in rural areas or even tier II or III cities, phenotypic methods are sometimes preferred for ESBL detection, resulting in false negatives. In a study from Indore, a city in central India, Bajpai *et al.* (2017) evinced the existence of ESBL genes like TEM, SHV, and CTX-M in a relatively high percentage of EPE isolates

(52.5 %) which had previously presented a negative phenotypic test [149]. These local studies must be adequately funded for the improvement in the detection of clinically relevant genes like ESBLs, which is vital for a fast diagnosis and prevention of fatal treatment errors. The extent of uropathogenic VIM and NDM-1 dissemination in northern India was put forward by Mohan *et al.* (2015) wherein the samples collected in 2008, there was a clear dominance of VIM at 43.6 % and NDM-1 at 0%. In 4 years, those numbers changed drastically to 24.4 % for VIM and 53.4 % for NDM-1, signifying the frightening increase in the mobility of these endemic genes [150]. In a publication that came out 2 years later from Delhi, Grover *et al.* (2017) showed how ESBL-producing*E. coli* can simultaneously synthesize NDM variants like NDM-1, NDM-4, and NDM-8, respectively [151]. This study provided supportive data with regardtoanother study published in 2014 from Lucknow, where the authors had indicated the emergence of novel NDM variants NDM 5 – 7 [152] in CRE. The fact that most UTIs originate in the community and then make their way into the north Indian hospitals [153] calls for stringent measures from the local authorities, especially from the perspective of antibiotic stewardship, in the management of community spread of ESBLs, leading to high degrees of co-resistance [154].

At the beginning of the last decade, carbapenem resistance was low in Southern Indian hospitals and antibiotics like meropenem were effective choices in treating UTIs caused by enterobacteria [155]. This meant that the dissemination of carbapenemase genes was low both in the clinics as well as in the community. A few years later, in 2018, a paper by Mahalingam *et al.* (2018) reported a significant increase (57 %) in the spread of carbapenemase genes like NDM and OXA from patients suffering from UTIs [156]. The presence of multiple ESBL genes like TEM and CTX-M, clubbed with NDM variants in specific isolates, incited concern. In a 5-year time frame, two studies from Bangalore and Tiruchirapally reported high nosocomial ESBL burdens in GNB at 64.4 % and 84 % [157, 158], probably due to the increased spread of the MGEs via urine. Two molecular epidemiological studies targeted towards understanding the threats posed by EPE and CRE in antenatal women from hospitals in Puducherry and Hyderabad deserve special mention, as it is well established that asymptomatic bacteriuria due to physiological and morphological changes in the female reproductive system during pregnancy may result in maternal and fetal morbidity/mortality [159]. The first study by Kalaivani *et al.* (2018) showed that from 271 isolates, 37 % were ESBL producers, predominantly expressing CTX-M-15 (58 %) [160]. A mere 4 % of all isolates produced SHV-1. Kammili *et al.* (2020) published a similar paper but with more information on the resistance status of the isolates [161]. From a sample of 133, 85 % of primigravid women were found to be infected with GNB. *E.coli* and *K. pneumoniae* were the most prominent EPE, accounting for 65 % and 41 % of all the GNB. In contrast to the previous study, TEM-1 was the most prevalent ESBL reported, present in 66.7 % of all the EPE followed by CTX-M-15 at 33.3 %. A high percentage of the ESBL producing *E. coli* were harborers of quinolone resistance genes *qnrS* and *aac(6')-Ib-cr*, hinting at a role of class I and class II integrons in the dissemination of these genes in the region [162].

In the Eastern state of Orissa, the rise in the prevalence of ESBL and MBL genes in uropathogens was reported by Jena *et al.* in 2013 [163]. What made the study unique was the fact that they reported the highest ESBL and MBL burdens in two uncommon uropathogens, namely *E. cloacae* and *Citrobacter* sp. (75 % for both organisms). According to their data, 51.78 % and 17.85 % of all the isolates were ESBL and MBL producers, respectively, which, at that time, was a comparatively high number w.r.t. similar studies [164]. The same team published a study in 2017 where the percentage of ESBL producers went up by 16.97 % with TEM being the commonest ESBL [165]. From Kolkata, Mukherjee *et al.* (2013) raised serious concerns over the declining efficacies of the third-generation cephalosporins in treating ESBL-producing MDR *E.coli*,as 45 % of test isolates didn't show sensitivity towards cefotaxime, ceftazidime, and ceftriaxone [166]. They highlighted the importance of such antibiotic surveillance and susceptibility studies from eastern India, for a proper understanding of the similarities and differences in the MDR nature of the isolates from the rest of India and abroad. Following suit, Borah *et al.* (2016) reported the incidences of nosocomial UTI caused by ESBL and MBL-positive*K. pneumoniae* and *E. coli* from Guwahati, Assam [167]. They employed techniques like multiplex polymerase chain reaction (PCR) to infer that *K. pneumoniae* was the most predominant organism in NDM dissemination in the region, beating *E. coli* by a large percentage margin. Both *E. coli* (62.5 %) and *K. pneumoniae* (33.3 %) were found to co-produce ESBLs along with NDM. The plasmid-borne CTX-M was the most common ESBL whereas SHV was found to be least frequent. One specific isolate (although not mentioned which) was reported to harbor all three ESBLs under investigation, along with NDM, which is disturbing, to say the least. Even with studies having larger sample sizes, the percentages of carbapenemase-producing GNB in the region never rose above 18 %. Banerjee *et al.* (2017) and Gajamer*et al.* (2019) reported 15.97 % and 9.04 % CRE and

carbapenemase-producing GNB respectively [168, 169]. The studies reported reasonably varying ESBL loads at 64.78 % and 13.66 %, which may very well be due to the differences in climatic conditions between Kolkata and Sikkim/Siliguri. Gajamer and team went a step further to show that a large percentage of the ESBL producers also co-produced carbapenemases like OXA-48, IMP, VIM, and NDM-5, disseminated via plasmids of incompatibility type HI1, I1, FIA+FIB, FIA, and Y. Similar modes of ESBL mobility was reported by this very team which was previously published in 2018 as the first report of phenotypic and molecular characterization of ESBLs from uropathogens like TEM, CTX-M, OXA-2, and SHV-76 from Sikkim and Darjeeling [170].

In Western India, carbapenems like imipenem were reported as potent biocides at the beginning of the last decade [171]. Even with high occurrences of EPE as well as ESBL-producing GNB, aminoglycosides like amikacin and imipenem remained effective against most hospital-borne MDR uropathogens. By 2014, the situation seemingly changed for the worse. In a study published from Pune by Khajuria *et al.*, the first cases of *E. coli* co-producing NDM-1 and OXA-48 (55 %) were reported from India [172]. Most of the isolates also produced ESBLs like CTX-M, TEM, SHV, and OXA. Unsurprisingly, both the NDM-1 and OXA genes were found to be located in plasmids, guaranteeing rapid transmissibility. Even then, the EPE has been identified as the main threat in the region, like the ST131 clone of *E. coli*. The particular pandemic fluoroquinolone co-resistant *E.coli* strain studied in a Pune hospital [173] showed its clonal relatedness to the isolate from the UK and was found to possess up to 6 plasmids in a single isolate (3 plasmids on average). None of the isolates were found to produce carbapenemases. High susceptibilities reported towards imipenem and meropenem in recent reports indicate that, in all probability, the spread of carbapenemase genes in the region has been low [174]. Unfortunately, the scarcity of papers from the region regarding the EPE and CRE transmissibility prevents us from reaching any evidence-based conclusion. Thus, studies similar to Khajuria *et al*. have no follow-up reports, making them futile.

5.3 From various infections:

Most hospitals report the pathology results from a cumulative set of samples, like blood, pus, urine, sputum, endotracheal aspirates, etc, collected from various departments and wards. Although it gives an overall estimate of the pathogen load in the samples taken together, in most instances, the analysis of AMR is not discrete w.r.t. the exact nature of an infection. Nevertheless, the data provide valuable information regarding the spread of resistance genes under investigation. By 2010, it was well established that ESBL genes like CTX-M were spreading rapidly via IS elements like IS21 in northern India [175]. Reports of rising ESBL and carbapenem resistance in *Enterobacteriaceae* were being published from the region, including cases of ESBL co-production [176, 177]. This rising resistance to high-end β-lactams clearly outlined the predisposing risks of getting admitted to ICUs, as Azim *et al.* reported a considerably high CRE (31.37 %) and EPE (92 %) load from an ICU in Lucknow [178]. In support, studies from centers in Varanasi indicated an increase in NDM-1 occurrence by 2% in ICUs in 2 years, being mobilized via class I integrons [179, 180]. The increase in CRE from 11 % (day 1) to 22 % (day 4) in ICU commensals was a clear indication of how genes like NDM-1, OXA-181, OXA-48, and KPC were ending up in pathogens [181]. Studies from Delhi, reporting fluctuating CRE values at 24.3 % and 65.1 %, agreed at one specific point, i.e., NDM-1 was the most widely disseminated carbapenemase in the region, while OXA, VIM, KPC, etc., are following suit at an uncomfortably rapid pace [182, 183]. By 2020, we have reports of 96 % EPE and 71 % load of NDM-1 from cities like Chandigarh [184], demanding immediate and strict action on behalf of the authorities.

In the south, amidst rising EPE cases, carbapenems were the go-to drugs [9]. In 2011, the high susceptibility of EPE towards drugs like imipenem [185]was corroborated by a low carbapenemase spread via clones as well as MGEs. In the meantime, ESBL genes (predominantly CTX-M) continued their spread unabated, reaching up to 77.3 % - 79.4 % [186, 187]. By the end of 2014, rising resistance towards carbapenems was being reported, reaching as high as 93.48 % against meropenem [188] with high KPC (67.4 %) and NDM (38.57 %) loads [188, 189]. The NDM-1 bearing isolates reached a ridiculous high of 72.7% - 81 % by 2017 [190, 191], resulting in increased patient mortality of 52 % [191]. Not only NDM-1, but OXA-producing*K. pneumoniae* was responsible for causing heavy infestations in certain pockets in Chennai [192]. 2020 onwards, *E.coli* variants like ST405 and ST410, bearing NDM-5 are clonally disseminating with haste, largely overshadowed by COVID-19 [193]. In 2021, the main challenge that lies in front of the public health administration is to tackle ESBL and carbapenemase-producing organisms parallel to the COVID management protocols that are in place, because the latest publications have reported nearly cent percent ESBL load in *K. pneumoniae*,along with CRE cases nearing 50 % [194, 195].

In a paper published in 2009 from Gangtok, Tsering *et al.* expressed serious concerns over the lack of

infrastructure in the northern fringes of eastern India for molecular-level interventions in ESBL and carbapenemase producers. They obtained phenotypic data that indicated a significant rise in ESBL transmission among different GNBs (34.03 %) in the region, especially *E. coli, K. pneumoniae*, and *C. Freundii*[196]. In a couple of years, it was becoming clear that the ESBL genes were disseminating rapidly among the enterobacteria like *E. coli*, which were also accumulating NDM genes in their cellular arsenal [197]. Although significant co-resistance between ESBL genes like TEM and CTX-M with NDM-1 was reported in *E. coli*, the incidences of carbapenem resistance in enterobacteria were relatively low at around 5% [198]. With increased use of expanded-spectrum cephalosporins in hospitals, novel variants of SHV genes, like SHV-148, have been found to associate themselves with gene cassettes like *IS26* and, resultantly, were horizontally transmitted in *E. coli*[199]. Even then, these organisms with low susceptibility towards third-generation cephalosporins remained controllable using drugs like imipenem [200] until recently, when an alarming phenomenon was unearthed. From Silchar in Assam, Paul*et al*. showed how *E. coli* were accepting carbapenemase genes like OXA-23 from other nosocomial pathogens like *A. baumannii* through $IncF_{rep}B$ and IncK plasmids [201]. The rare occurrence of the *A. baumannii* gene in *E. coli* gave a clear indication that, due to the higher effectiveness of the carbapenems, they were being used extensively in the hospital setting, providing the much-needed selection pressure for the emergence of carbapenem resistance in previously susceptible organisms. By 2019, both ESBLs and carbapenemases had disseminated extensively in the region, as evidenced from recent publications [202, 203]. The Rising cases of NDM-1-positive*K. pneumoniae* and *E. coli* (45.2%), along with ESBL-ESBL-carbapenemase co-resistance (24.73 %),warrant extensive antibiotic surveillance and follow-up in Eastern India for the containment of these resistant clones to preserve the efficacy of the carbapenems.

Compared with the other regions, the western part of India has reported low ESBL percentages in 2008 [204]. The authors claimed that at 22%, the incidence of EPE was less compared with other hospitals in the country. In the same year, NDM-1 carbapenemase was discovered in India, prompting researchers to look for these genes in nosocomial gram-negative pathogens. The rapid endemic spread of the NDM variants in a very short period was evident from the results obtained by Deshpande *et al*. 91.67 % of all the *Enterobacteriaceae* isolates they investigated contained the NDM gene, mostly in *Klebsiella* spp., the genus in which the gene was first detected [205]. These results could not be reproduced by any other team in the country. Even in a busy city like Mumbai, the percentage of CRE hardly went above 13% [206] till 2013. The scenario changed in 2014 when CRE bearing NDM-1 (75.22%) and OXA (4.42%) emerged in Mumbai [207] hospitals. No other significant studies on CRE, including follow-ups of the mentioned reports, exist. There is a serious shortage in the literature reporting these organisms from western India and this review aims to attract the attention of the concerned personnel. With such a dearth of knowledge regarding the status of the EPE and CRE in the region, it must be difficult to design treatment strategies against these organisms, leading to further AMR acquisition.

Some other relevant papers that could not be discussed in the main text are placed in Table 2.

Table 2: Recent and relevant publications regarding EPE and CRE from India:

S. No.	Zone	Year of publication	Organisms detected	Resistance shown	Reference
1.	North/Central India	2007	EPKP	TEM, SHV	[208]
2.	North/Central India	2010	EC, KP	CTX-M-15, TEM, SHV	[209]
3.	North/Central India	2012	EC, KP	Phenotypic ESBL producer	[210]
4.	North/Central India	2013	EC, KP	Phenotypic ESBL and MBL producer	[211]
5.	North/Central	2014	EC, KP	Phenotypic ESBL producer	[212]

	India				
6.	North/Central India	2014	EC	Phenotypic ESBL producer	[213]
7.	North/Central India	2014	EC, KP	Phenotypic ESBL producer	[214]
8.	North/Central India	2017	EC, KP	Phenotypic ESBL and carbapenemase producer	[215]
9.	North/Central India	2019	EC	NDM-1, IMP, VIM, OXA-46, KPC	[216]
10.	North/Central India	2019	CRE	NDM-1, NDM-5, VIM, OXA-48	[217]
11.	Northern and Southern India	2017	EC, KP, K, E	TEM, CTX-M. VEB, OXA-1, NDM-1	[218]
12.	Northern and Southern India	2019	EC, KP	TEM, OXA-1, CTX-M-1, CTX-M-2, CTX-M-15, SHV, Phenotypic carbapenemase producer	[112]
13.	Southern India	2012	EC, PM, K	Phenotypic ESBL producer	[219]
14.	Southern India	2016	EC, KP	TEM, OXA, SHV, CTX-M-1	[220]
15.	Southern India	2016	EC	CTX-M	[221]
16.	Southern India	2016	EC, KP	Phenotypic carbapenemase producer	[222]
17.	Southern India	2017	EC, KP, CF, ECL	NDM, OXA-181, VIM	[223]
18.	Southern India	2018	KP	KPC-2	[224]
`19..	Southern India	2019	EC	CTX-M	[225]
20.	Southern India	2019	EC, KP, K, KO	OXA-48, NDM, KPC, VIM	[226]
.21.	Southern India	2019	KP	NDM-1	[227]
22.	Southern India	2020	EC, KP, C, PM	CTX-M	[228]
23.	Eastern India	2012	EC, KP	Phenotypic ESBL producer	[229]
24.	Eastern India	2012	KP	TEM-1, TEM-116, SHV-11, CTX-M-72	[230]
25.	Eastern India	2015	EPE + other GNBs	PER-1	[231]
26.	Eastern India	2017	EC	CTX-M, SHV, TEM, OXA	[232]
27	Western India	2013	EC, KP	TEM, SHV, CTX-M	[233]
28.	Western India	2015	EC, KP	Phenotypic ESBL and carbapenemase producer	[234]

6. Conclusion:

The review is a testament to the fact that ESBLs and carbapenemases, belonging to one of four molecular classes of β-lactamases, are being rapidly disseminated by the members of the *Enterobacteriaceae* family in the Indian hospital setting. At a time when India spends only 4.7 % of its Gross Domestic Product on health, with a governmental share of 1.15 % [235], there is a huge mountain to climb for the Indian health administration in curbing AMR. A few salient areas where the state and central governments must work together to minimize the emergence and dissemination of the ESBLs and carbapenemases are:

1. Increased fund allocation for the possibility of carrying out molecular-level investigations of nosocomial pathogenic *Enterobacteriaceae* and GNBs for rapid detection of the deleterious genetic determinants is the key.
2. Strict antibiotic stewardship and surveillance on prescriptions and sales are warranted. All tiers of healthcare, i.e., primary, secondary, and tertiary health centers, must fall in the surveillance and monitoring purview.
3. Judicious use of antibiotics on animals, including aquaculture, must be ensured.
4. Proper sewage management is vital, especially referring to the hospital wastes that have a high chance of contamination with sub-lethal levels of residual antibiotics as well as MDR organisms. Periodic assessments of the hospital effluents must be performed to check the residual antibiotic levels as well as the pathogenic load.
5. The dumping of hospital and industrial (mainly pharmaceutical) wastes onto nearby lakes and rivers must be prevented.
6. Community-level education programs must be organized by the governmental/non-governmental bodies for the masses, to make them aware of the perils of AMR.
7. Reporting of EPE and CRE must be made mandatory for all hospitals, both rural and urban, from all parts of the country. The facilities must be funded adequately so that they can train their staff and carry out the detection of ESBL and carbapenemase genes in-house. The early detection of endemic variants of genes like NDM, OXA, CTX-M, or any other ESBL/carbapenemase will become vital for the preservation of the efficacy of high-end β-lactam antibiotics.

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